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09/121,798	07/23/1998	ROBERT BRIDENBAUGH	018484-00120	3701

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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	21

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/121,798	Applicant(s) Bridenbaugh et al
	Examiner William Sandals	Art Unit 1636

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Oct 9, 2001*.

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-21* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [ ] Notice of References Cited (PTO-892)

16) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). *18*

18) [ ] Interview Summary (PTO-413) Paper No(s). _____

19) [ ] Notice of Informal Patent Application (PTO-152)

20) [ ] Other:

DETAILED ACTION

Response to Arguments

1. Arguments set forth in Paper No. 20, filed October 9, 2001 regarding the rejection of claims 14-16 under 35 USC 112, second paragraph have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

2. Arguments set forth in Paper No. 20 regarding the rejection of claims 1-21 under 35 USC 103, have been fully considered but they are not persuasive. The response to the arguments is contained in the rejection repeated below.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 18-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 6,011,148. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only substantial differences between the claimed invention and that disclosed by US Pat. No. 6,011,148 is the use of static mixers in the plasmid isolation prior to the use of ultrafiltration and or anion exchange chromatography in a plasmid procedure that can be readily automated. A response in Paper No. 20 indicates that a terminal disclaimer will be filed upon indication of allowance. The rejection remains for reasons of record.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 14-16 are drawn to the simultaneous performance of steps (a)-(d), (a)-(e) and (a)-(f) respectively. It is not clear from the claims or text of the specification how one of skill in the art would carry out a mixing step in a flow through mixer, a centrifugation step and a neutralization step simultaneously. It would appear that the steps are mutually exclusive, and each step would require separate equipment which would be difficult if not impossible to combine for the simultaneous performance of all three steps.

Response to Arguments

7. Arguments set forth in Paper No. 20 assert that the steps of the invention can be carried out simultaneously. The argument centers on the concept of the word simultaneously. The specification teaches a continuous process where a large volume of solution is processed by passing the solution through a series of connected pieces of apparatus. With these limitations set forth, it is possible to construe that the entire volume of solution being processed is one sample. Given this construction of limitations, it is possible to conceive of the steps being carried out simultaneously on a single large volume of solution. However, a continuous process practiced on a single large volume sample in a series of process steps is not claimed. The language of claims 14-16 does not set forth limitations which are clear as to how to perform each step simultaneously. Therefore, the argument is not found convincing and the rejection is sustained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 517,515 A2 in view of US 6,197,553 B1 (of record), US 5,837,529 (of record) and Song et al.

The claims are drawn to a method for purifying at least about 100 mg. of plasmid DNA for pharmaceutical use by mixing the DNA and an alkaline lysing agent in a static mixer, then adding a precipitation agent in a second static mixer, removing the precipitated component by centrifugation, neutralizing the solution, and passing the clarified solution over an ion exchange column. An ultrafiltration step may be performed before the ion exchange step.

EP 517,515 A2 taught (see the entire patent application) a method for purifying large quantities of plasmid DNA for pharmaceutical use by mixing the DNA and an alkaline lysing agent, neutralizing, removing the precipitated component by filtration followed by an ultrafiltration step. EP 517,515 A2 discusses the obvious and well known use of Rnase digestion and potassium acetate in the process.

EP 5,157,515 A2 did not teach a precipitation step, a centrifugation step, or an ion exchange column step.

US 6,197,553 B1 taught (see especially the abstract and columns 1-6) the purification of large quantities of plasmid for pharmaceutical use by a heat lysis step in a flow-through heat exchanger, followed by a centrifugation step, followed by a filtration step, followed by an ultrafiltration step, followed by an ion exchange step. The specific flow rates cited in the claims are merely optimizations of the method and are not patentably distinct.

US 5,837,529 taught (see especially the abstract, figures and columns 2-4) a method for purifying large quantities of plasmid DNA for pharmaceutical use by mixing the DNA and an alkaline lysing agent in a static mixer, then adding a precipitation agent in a second static mixer.

Song et al. taught (see especially the abstract, introduction, page 3390, column 2, bottom, figures 1-4, page 3394, column 1, top, and the discussion at page 3396, column 2) the general theory of concentration polarization on a membrane during ultrafiltration. Song explains that the process of ultrafiltration involves the development of a polarization layer of the solute (in the instant claimed invention, the solute is the plasmid and other cell lysate products being purified, diafiltered and concentrated) on the ultrafiltration membrane, which provides a resistance to flow through the ultrafilter. The presence of this layer on the ultrafilter provides a "packed" layer of solute, or "gel layer", through which all other solute present in the solution must pass or else will be retained in the solution. This "gel layer" of "packed" solute on the ultrafilter provides a second layer for filtration, as discussed by Song et al. in the introduction, at page 3390, column 2, bottom, further demonstrated in figures 1 and 2, and then at page 3394, column 1, top. The practical aspects of managing a gel layer in ultrafiltration is a consideration of solute concentration versus pressure which controls the amount of gel layer formed on the ultrafilter. The presence of "gel layer" on an ultrafiltration membrane is therefore an inherent aspect of ultrafiltration, and the physical retention of solute in an ultrafiltration process will always involve the development and management of the "gel layer".

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the method for purifying large quantities of plasmid DNA for pharmaceutical use of EP 517,515 A2 with the method for purifying large quantities of plasmid DNA for pharmaceutical use of US 6,197,553 B1 and US 5,837,529 because they were all

involved in the process of purifying large quantities of plasmid DNA for pharmaceutical use. Song et al. provides the theoretical background on the formation of a "gel layer" in an ultrafiltration process.

One of ordinary skill in the art would have been motivated to combine the method for purifying large quantities of plasmid DNA for pharmaceutical use of EP 517,515 A2 with the method for purifying large quantities of plasmid DNA for pharmaceutical use of US 6,197,553 B1 and US 5,837,529 because EP 517,515 A2 taught (see column 2, lines 25-37) that the alkaline lysis method of bacterial cell lysis may be used as an equivalent to the heat lysis method of US 6,197,553 B1. US 6,197,553 B1 recites at column 2, lines 39-42 "recent advances in the field of polynucleotide-based vaccines for human use, and potentially human gene therapy, requires the ability to produce large quantities of the polynucleotide vaccine in purified form". Then at column 4, lines 43-56 state "preparative scale chromatography is a powerful purification tool that provides high resolution, operational ease and increased productivity for purifying DNA plasmid products....chromatography steps achieve separations between various forms of plasmid (supercoiled, open, relaxed, linear and concatamers) and remove host contaminants like LPS (endotoxin), RNA DNA and residual proteins". US 5,837,529 states at column 2, bottom, bridging to column 3, top that the static mixers provide a distinct advantage for lysing large quantities of bacterial cells for the production of plasmids over other methods. Song et al. provides the theoretical background on the formation of a "gel layer" in an ultrafiltration process. Further, a person of ordinary skill in the art would have had a reasonable expectation of success

in the producing the instant claimed invention given the teachings of EP 517,515 A2 with US 6,197,553 B1, US 5,837,529 and Song et al.

Response to Arguments

10. Arguments presented in Paper No. 16, filed March 20, 2001 assert that US 6,197,553 does not teach the alkaline lysis step of the instant claimed invention and that US 6,197,553 seems to teach away from the alkaline lysis step. EP 517,515 A2 provides the teaching that the heat lysis step of US 6,197,553 is equivalent to the alkaline lysis step of EP 517,553. US 6,197,553 teaches away from an alkaline lysis step which involves the use of materials in the step which would be toxic to the ultimate human consumer. EP 517,553 teaches an alkaline lysis step which does not employ the toxic materials and therefore, the objections to an alkaline lysis step which appear to "teach away" are moot.

11. In response to applicant's argument in Paper No. 16 that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

12. In response to applicant's argument presented in Paper No. 16 that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is clearly stated in the rejection above where each of the references of US 6,917,553 and US 5,837,529 recite that the additional steps which they teach are advantageous for the process of purifying large scale plasmid DNA preparations for pharmaceutical use and their combination is therefore obvious.

13. Arguments set forth in Paper No. 20 assert that there is no teaching of a neutralizing step in the teachings of EP 517,515 A2, US 6,197,553 B1, US 5,837,529 and Song et al. The previous office action was quoted as stating that no teachings were found in the cited prior art. The assertion is not correct and the previous office action was not accurate. EP 517,515 taught at page 2, column 1, lines 11-12 and again at page 2, column 2, lines 25-30, that a neutralizing step is indeed performed. The neutralizing step was inadvertently referred to as a precipitating step in the previous office action. This obvious error has been corrected in the instant rejection.

14. Arguments are set forth in Paper No. 20 assert that EP 517,515 taught a laboratory scale process and did not teach a scaled up process. EP 517,515 is silent on the scale of the process. The process steps of EP 517,515 are the same steps used in the instant claimed invention, which would make them applicable to large scale production. It therefore follows that the teachings of the instant specification support the enablement of the use of the process of EP 517,515 in a large

scale process. EP 517,515 taught that the method is useful in the field of genetic engineering. Since the process is contemplated for preparation of DNA for use in genetic therapy in humans, the teachings of EP 517,515 do not teach away from the recited process of EP 517,515 being used on a large scale, and in fact point toward a large scale manufacturing process.

15. Arguments are set forth in Paper No. 20 assert that EP 517,515 did not teach that alkaline lysis and heat lysis were equivalent. EP 517,515 taught that alkaline lysis or heat lysis may be used as alternatives. While there is no specific text in EP 517,515 teaching that the two method steps are equivalent, EP 5157,515 teaches the use of either method step as being interchangeable. The interchangeable aspect of the alkaline lysis step and the heat lysis step makes the method steps equivalent for the purposes of the instant claimed invention.

16. Further arguments are set forth in Paper No. 20 assert that EP 517,515 did not teach that the method steps which follow the lysis step are the same. EP 517,515 taught that either lysis method may be used as the first step, which is then followed by the second and subsequent steps, all steps which follow the lysis step are the same.

17. Arguments are set forth in Paper No. 20 assert that US 6,197,533 teaches away from the teachings of EP 517,515, where a method used in a small scale process are problematic for use in a large scale process. US 6,197,533 recites 7 process steps which can be problematic in large scale processes. Of the 7 process steps which US 6,197,533 taught to be problematic, EP 517,515 used one of the 7 steps recited to be a problem in scale up which is the alkaline lysis step. However, US 6,197,533 also taught that the use of lysozyme was one of the 7 process steps

which can be problematic, and then proceeds to teach the use of a lysozyme step in the method. Therefore, one of ordinary skill in the art would recognize that each problematic step must be weighed for its advantages over its disadvantages. EP 517,515 taught either the alkaline lysis method step or the heat lysis step may be used. US 6,197,533 uses the heat lysis method step as an alternative to the alkaline lysis step. This being the case, US 6,197,533 did not teach away from EP 517,515, rather it taught the same method steps which were also taught by EP 517,515.

18. Arguments are set forth in Paper No. 20 assert that by the fact that each of EP 517,515 A2, US 6,197,553 B1, US 5,837,529 and Song et al. teaches that their method produces suitable plasmid DNA infers that no additional method steps are necessary. None of EP 517,515 A2, US 6,197,553 B1, US 5,837,529 and Song et al. state that no additional method steps are necessary. Each of EP 517,515 A2, US 6,197,553 B1, US 5,837,529 and Song et al. teach methods which are congruently connected, and each contains method steps taught by the other, which leads to the obvious combination of methods to produce the instant claimed invention.

19. Arguments are set forth in Paper No. 20 assert that Song et al. is a theoretical paper which has no bearing on the practice of a method of purifying a plasmid. It is asserted that inherency is no substitute for some teaching or suggestion to combine. The theoretical teachings of Song et al. are used to make clear the fact that a gel layer formation is a fundamental physical fact that arises from the process of ultrafiltration, and that any macromolecule, plasmid DNA included, must follow the laws of nature. The formation of the gel layer is a principle of ultrafiltration, and citing it as a patentably distinct feature does not follow. The teachings of the specification set

forth the parameters where a gel layer can be used as part of a process of ultrafiltration, which must conform to the physical principles set forth in Song et al.

20. In response to applicant's argument in Paper No. 20 that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
December 20, 2001

TERRY MCKELVEY
PRIMARY EXAMINER